

ADVERSE DRUG REACTION

Ulcerative colitis after statin treatment

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Statin treatment is widely used in both primary and secondary prevention of diseases in which hyperlipidaemia is a major risk factor, for example, ischaemic heart disease. The development of ulcerative colitis as an adverse reaction to simvastatin is reported, which, despite withdrawal of the drug, proved fatal. The adverse reaction profile of the statins is reviewed, which suggests that this is a class effect and not one limited to simvastatin.

There is increasing evidence to support the use of lipid lowering treatment in patients with significant risk of coronary artery disease and a total cholesterol concentration above 5 mmol/l.¹ Significant side effects from lipid lowering treatment are rare: the most widely reported being muscle toxicity, including rhabdomyolysis, which is usually reversible when treatment is discontinued.² We report the development of extensive ulcerative colitis in relation to treatment with simvastatin, discuss the previous data for all the statin agents, and suggest a possible mechanism.

CASE REPORT

A 65 year old man was referred to the medical admissions unit at our hospital with a one month history of diarrhoea, passing between five and 10 loose, watery motions per day, occasionally with blood. There was no associated abdominal pain or bloating and he stated that he had not lost any weight. There was a previous history of ischaemic heart disease, with a myocardial infarction in 1996 and hypercholesterolaemia.

The patient had had one similar episode, approximately one year before admission. On that occasion, it was felt by his general practitioner that the episode coincided with the patient starting pravastatin. His total serum cholesterol was 6.4 mmol/l. The pravastatin was discontinued and the patient's symptoms resolved.

At the time of admission, the patient was taking aspirin 75 mg and atenolol 50 mg once a day, enalapril 5 mg twice a day, and simvastatin (Zocor, Merck Sharp & Dohme (MSD), Hod-desdon, Herts, UK) 20 mg once a day. He had been started on simvastatin 10 mg once a day, six months before admission, apparently without ill effect. Because the serum cholesterol remained raised at 5.6 mmol/l, this had been increased to simvastatin 20 mg once a day one month before admission; shortly afterwards, the symptoms had started.

On examination, he was dehydrated with a temperature of 38.1°C. His pulse was 70 beats/min and regular. Abdominal examination revealed only mild distension and normal bowel sounds were heard on auscultation. Rectal examination revealed generalised tenderness with a small amount of fresh blood.

Investigations showed a raised serum urea concentration (9.5 mmol/l). A full blood count showed reduced haemoglobin at 119 g/l with a mean corpuscular volume of 85 fl, and a white cell count of $4.5 \times 10^9/l$ with a normal differential. Serum albumin was low at 24 g/l. An abdominal radiograph showed occasional dilated bowel loops. There were no features of megacolon.

The simvastatin was discontinued. A flexible sigmoidoscopy was performed which showed "fulminant" proctitis and colitis. Biopsies later confirmed a diagnosis of ulcerative colitis. Treatment was started with intravenous hydrocortisone 100 mg four times a day and bowel "rest", with good clinical benefit.

However, on day 5 of admission, the patient had significantly more abdominal pain. Examination showed a pulse rate of 84 beats/min and a temperature of 36.8°C. He had a very tender abdomen with guarding and absent bowel sounds. Abdominal film showed features consistent with toxic megacolon.

Emergency laparotomy was performed, at which the findings were recorded as "...megacolon, with necrosis at the splenic flexure and multiple small perforations...". Panproctocolectomy was performed and an ileostomy constructed. Histology of the resected specimen confirmed severe ulcerative colitis with ulceration and polyp formation throughout. There was no evidence of malignancy. Postoperative care was provided on the intensive care unit.

By day 10, there was little improvement, with ongoing systemic hypotension, despite pressor support. The stoma was noted to be dusky in appearance and laparotomy was again performed. On this occasion the findings were "Necrotic ileostomy; free pus in the peritoneum with multiple abscesses between the bowel loops...". Peritoneal lavage was carried out with subsequent refashioning of the ileostomy. The patient was transferred back to the intensive care unit, but developed multiple organ failure despite maximal support. Twelve days after admission, he died. No postmortem examination was performed.

DISCUSSION

The summary of product characteristics for simvastatin (Zocor) includes the following side effects: reversible myositis, headache, altered liver function tests (rarely, hepatitis) and *gastrointestinal effects including abdominal pain, flatulence, diarrhoea, nausea, and vomiting*. Rash and hypersensitivity reactions have been reported rarely; also alopecia, anaemia, dizziness, paraesthesia, peripheral neuropathy, jaundice, and pancreatitis.²

While ulcerative colitis is not listed as a side effect of simvastatin, the manufacturer, MSD, confirms that, up to May 2001, there have been six cases of colitis attributed to its use (four cases of ulcerative colitis,^{2,3} one case of collagenous colitis,⁴ and one not otherwise specified) and two further cases of pre-existing ulcerative colitis exacerbated by simvastatin treatment.² Diarrhoea, not otherwise specified, has been reported in a further 114 patients, compared with 96 reports of myositis.²

This problem does not appear to be limited to simvastatin. At the time of writing, the Committee on Safety of Medicines/Medicines Control Agency have received one report of ulcerative colitis and three reports of colitis suspected to be associated with pravastatin, and one report of colitis aggravated in association with atorvastatin.² There is also one report of inflammatory bowel disease (not otherwise specified) for fluvastatin.²

Learning points

- Colitis is a rare complication of simvastatin treatment.
- Colitis may be an effect of all statins.
- Always consider drugs as a possible cause of new symptoms.
- Remember to report all significant side effects (causing or prolonging hospitalisation or causing death) for all drugs, irrespective of the length of their product licence.

The mechanisms through which the statins cause diarrhoea and colitis may relate to their non-lipid lowering effects. There is evidence to suggest that nitric oxide acts at inhibitory nerves in the colon producing impaired gut motility in patients with ulcerative colitis.⁵ The statins, in turn, have been shown to upregulate endothelial nitric oxide synthase and, as a consequence, increase the levels of nitric oxide in tissues.^{6,7} In addition, statins have been shown to stimulate the production of various cytokines, notably tumour necrosis factor- α , interleukin (IL)-6, and IL-8.⁸ Increased production of these last three proinflammatory cytokines are linked with increased disease activity in patients with ulcerative colitis,⁹ and it may be that statin treatment reveals previously quiescent colitis in susceptible individuals.

This would appear to be a rare side effect of statin treatment, but one which, like other adverse drug reactions, is almost certainly subject to under-reporting. As it appears to be a class effect, we would suggest using alternative lipid lowering treatments in patients experiencing such effects. We have not been able to find any such reports for the fibrate group of drugs. Moreover, there is evidence to suggest that bezafibrate can suppress chemically induced colitis in rats.¹⁰

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